HHS Public Access

Author manuscript

J Pediatr Rehabil Med. Author manuscript; available in PMC 2016 October 12.

Published in final edited form as:

J Pediatr Rehabil Med. 2015 ; 8(4): 297–308. doi:10.3233/PRM-150348.

Increased brain activation during working memory processing after pediatric mild traumatic brain injury (mTBI)

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Abstract

Purpose—The neural substrate of post-concussive symptoms following the initial injury period after mild traumatic brain injury (mTBI) in pediatric populations remains poorly elucidated. This study examined neuropsychological, behavioral, and brain functioning in adolescents post-mTBI to assess whether persistent differences were detectable up to a year post-injury.

Methods—Nineteen adolescents (mean age 14.7 years) who experienced mTBI 3–12 months previously (mean 7.5 months) and 19 matched healthy controls (mean age 14.0 years) completed neuropsychological testing and an fMRI auditory-verbal N-back working memory task. Parents completed behavioral ratings.

Results—No between-group differences were found for cognition, behavior, or N-back task performance, though the expected decreased accuracy and increased reaction time as task difficulty increased were apparent. However, the mTBI group showed significantly greater brain activation than controls during the most difficult working memory task condition.

Conclusion—Greater working memory task-related activation was found in adolescents up to one year post-mTBI relative to controls, potentially indicating compensatory activation to support normal task performance. Differences in brain activation in the mTBI group so long after injury may indicate residual alterations in brain function much later than would be expected based on the typical pattern of natural recovery, which could have important clinical implications.

Keywords

Concussion; Mild Traumatic Brain Injury; mTBI; Pediatric; Functional Magnetic Resonance Imaging; fMRI; Working Memory

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Statement of Conflict of Interest

The authors have no conflicts of interest to declare.

1. Introduction

Concussion or mild traumatic brain injury (mTBI) has become a significant public health concern, with recent increased attention to pediatric concussion, notably in organized sports. Of particular interest are the specific effects of injury in pediatric populations because of ongoing neural development and potential for long-term cognitive and behavioral consequences. Recent CDC estimates are that 315,300 children age 10–19 experience a TBI annually [1]. An epidemiological study of pediatric TBI incidence found 304 cases per 100,000 child-years in children under age 18; of these about 97% were mTBI [2]. Another study found 2,112 treated pediatric concussions between the years of 2006–2011 within one emergency department, with a higher proportion being males (67%) and nearly half being sports-related (48%) [3]. With increased public awareness and the relatively high incidence of injury, better understanding of potential sequelae of mTBI and their neural substrate is needed. While most individuals experience symptom resolution relatively rapidly [4, 5], a growing amount of data is now establishing significant sequelae from even minor injuries in a subset of individuals, and suggests that children and adolescents may take longer to recover from injury than adults [6–10].

Acute cognitive effects of mTBI examined using neuropsychological testing have been widely explored, with deficits frequently found in executive functioning [4, 11, 12]. These deficits typically resolve within weeks to months [4, 13, 14], and a pediatric population study showed significant improvements in a two-year follow-up [12]. Persistent post-acute effects of pediatric mTBI are less well understood. One recent study found reduced performance enhancement over time on executive function tasks [15]; that is, control participants showed significantly greater improvement in task performance than mTBI participants over 12 weeks post-injury. Catale et al. [16] found executive and attentional deficits one year post-injury in pediatric mTBI participants compared to controls. There is also evidence of age being important when considering recovery time, and younger individuals may need increased time to reach full recovery [17, 18]. Relative to controls, Baillargeon et al. [19] found persistent neurophysiological alterations in concussed children, adolescents, and adults at least six months post injury, and also found that adolescents exhibited persistent working memory decrements that were not apparent in children or adults, suggesting increased sensitivity to injury in this age range. Working memory is often categorized under the broader heading of executive functions, and can be conceptualized as the process of maintaining necessary information in short-term memory and manipulating it to conduct relevant operations [20, 21]. Working memory deficits are among the most common cognitive complaints after TBI of any severity, and can in turn contribute to problems in other aspects of cognitive, academic, vocational, and social functioning, and thus negatively impact quality of life [22].

Functional neuroimaging methods such as functional MRI (fMRI) have shown working memory to be subserved by a network involving frontal and parietal brain regions [23]. Findings after mTBI have been mixed; some studies in adults have shown increased [24, 25] or decreased [26–28] cerebral activation during working memory processing (see also [29] for review). To date there has been very little examination of brain functioning after pediatric mTBI using fMRI [30]. The limited available data have shown alterations in brain activation

and a relationship between activation and post-concussive symptoms during working memory processing in the subacute period after pediatric concussion [31–34], but such studies have generally not examined children further out from injury. Within the first three months after injury Krivitsky et al. [32] only observed differences in working memory-related fMRI activation between mTBI participants and controls when inhibitory demands were introduced, whereas Keightley et al. [31] found that concussed adolescents demonstrated worse working memory performance and reduced task-related activation. Studies of concussed adolescent athletes have found increased symptom severity and prolonged recovery from concussive symptoms to be related to differential patterns of brain activation during working memory processing [33, 34]. Given these mixed findings, and the limited available pediatric data examining brain functioning in the post-acute period after concussion/mTBI, the purpose of this study was to examine children and adolescents after the subacute period post-injury to assess whether residual differences in brain function were detectable on a commonly used fMRI working memory task.

2. Methods

2.1 Participants

Participants included 19 children and adolescents 3–12 months post-concussion/mTBI (the terms concussion and mTBI are often used interchangeably; here we will use mTBI to reference this group). Participants from both groups were recruited through community advertisements. mTBI participants were also referred by local clinicians. All mTBI participants had been diagnosed with concussion/mTBI by a sports medicine physician or other qualified professional. This diagnosis was confirmed by study staff during screening for this study based on participant/parent report and medical records when available, using the American Congress of Rehabilitation Medicine definition of mTBI [35]. Mechanism of injury was sports-related/recreational for 17 participants (football (6), hockey (3), softball/baseball (2), soccer (2), and one injury each from snowboarding, bicycle riding, track and field, and roller blading), with two participants injured in ATV accidents. Three mTBI participants reported brief loss of consciousness, and two were uncertain whether they lost consciousness. No mTBI participant reported history of prior injury of greater than mild severity by ACRM criteria, though 13 reported having had prior concussions (see Table 1 for subject-level detail regarding injury characteristics). Systematic data regarding current post-concussive symptoms were not available; presence/absence of such symptoms was not an eligibility requirement for study participation.

The healthy control group included 19 children and adolescents with no history of brain injury of any severity. Group level matching was conducted to ensure that there were no significant differences ($p > 0.05$) between the healthy control and mTBI groups for age, sex, estimated Full Scale IQ [36], maternal education, or 2-back task performance accuracy (see Table 2 for sample demographics, age range was 10–16 years for both groups; see Table 3 for N-back task performance). All participants were right-handed and were screened for routine metal and safety exclusions for participation in an MRI study (implanted devices, metal devices, etc.). Study eligibility criteria excluded participation in either group for individuals with history of significant medical, neurological, or psychiatric diagnosis, or

previously diagnosed learning or attention disorder. One mTBI participant was taking psychotropic medications at the time of study participation (Seroquel for sleep, Vyvanse for attentional symptoms). Analyses were repeated with and without this participant, without change in the overall pattern of findings. Written informed parental consent and participant assent was obtained for all participants according to the Declaration of Helsinki under a protocol approved by the Indiana University Institutional Review Board.

2.2 fMRI Working Memory Task

A block design auditory-verbal "N-back" task was used to evaluate working memory. The N-back paradigm has been demonstrated to be an effective and valid task for fMRI assessment of working memory [37, 38], and reliably elicits activation in bilateral frontal, parietal, cerebellar, and basal ganglia circuitry [29]. This task has been used by our research team for many years to examine alterations in working memory functioning after TBI [24, 25, 39–41]. During scanning, participants heard a series of consonant letters (except L, W, and Y) presented one every three seconds. Task conditions were 0-, 1-, and 2-back. Each condition was presented in 27-second epochs preceded by three seconds of instruction (e.g., "the match is one back"). For each letter, participants responded via button press to indicate whether the current letter was a match (i.e., was the same as the designated target or the letter presented one or two back in the sequence, depending on the condition) or a nonmatch. The three experimental conditions were each presented three times in pseudorandom order for a total of nine task blocks (task time 6:00). Participants practiced a version of the task before scanning to ensure comprehension of the task. Stimuli were presented through an MRI compatible headphone system, and Presentation software (Neurobehavioral Systems, Inc., Albany, CA) was used to program the task and record response accuracy and reaction times. Within-subject and between-group comparisons for fMRI task behavioral data (performance accuracy and reaction time) were analyzed using appropriate statistical tests (e.g., repeated measures ANOVA, independent-samples T-tests., etc.) using SPSS version 22.

2.3 Image Acquisition, Processing, and Analysis

Scans were acquired on a 3T Siemens Tim Trio scanner using a standard 12-channel head coil. Structural scans were acquired to rule out incidental pathology. For fMRI, a gradient echo, echo-planar BOLD sequence was employed with whole brain coverage: TR = 2250 ms, TE = 29 ms, FOV = 22 cm, NEX = 1, 39 interleaved 3.5 mm thick axial slices with no skip, 88 × 88 matrix, yielding 2.5 mm^2 × 3.5 mm voxels. Imaging data preprocessing and analyses were conducted in SPM8. In brief, after correction of slice timing, spatial realignment using a six-parameter model was performed on raw scan data to remove minor motion-related signal change. Realignment parameters were entered as covariates at the subject level, and all volumes were normalized into Montreal Neurological Institute atlas space, resampled to 2 mm^3 isotropic voxels, and smoothed to a FWHM of 6 mm. Contrast images comparing pairs of working memory load conditions were created for each participant using a block analytic approach for each task condition (i.e., 0-, 1-, and 2-back). For this investigation analyses focused on the most difficult task condition (i.e., the 2-back > 0-back contrast). These contrast images were then used in second-level multi-subject voxel-wise analyses. Voxel-wise random effects analyses for fMRI were conducted using a two-

sample T-test (between-group analysis) as implemented in SPM8 to construct maps of voxels in which activation differed as a function of group (mTBI and control). Voxel-level (peak) significance values represent the chance under the null hypothesis of finding a voxel with as great as or greater a height threshold (Z). Cluster-level significance can be interpreted as the probability under the null hypothesis of finding a cluster with as great as or greater a number of voxels, with family-wise error (FWE) correction for the whole-brain search volume (i.e., correction for multiple comparisons). Findings are reported at an overall $p_{crit} = 0.01$; only clusters with cluster-level $p_{FWE\text{-}corr} < 0.05$ were considered to be significant. Significant clusters were extracted using MarsBaR to conduct correlational analysis between brain activation, fMRI task behavioral data, and time since injury in SPSS version 22.

2.4 Neuropsychological Testing and Parent-Report Measures

The neuropsychological battery was designed to examine functioning across cognitive domains, but with a focus on executive functioning and memory, as these domains are most commonly reported to be affected after TBI. Tests were grouped into cognitive domains to reduce the number of statistical comparisons and the likelihood of type I error on the basis of expert neuropsychological opinion (B.C.M. and A.J.S.) and guided by a factor analysis, similar to the approach used in our other previous studies [42–44]. Raw neurocognitive test scores were normalized (z-transformed) using the mean and standard deviation of the control group scores. Domain scores were created for each participant by averaging the z-scores of the included tests. The memory domain included the California Verbal Learning Test-Children's Version (CVLT-C) [45] total raw score for trials 1–5 and short and long delay free recall raw scores; Children's Memory Scale (CMS) [46] stories immediate and delayed recall raw scores; CMS dot locations total, learning, and long delay raw scores; CMS faces immediate and delayed raw scores; and Rey Complex Figure Test (RCFT) [47] immediate and delayed raw scores. The processing speed domain consisted of the Delis-Kaplan Executive Function System (D-KEFS) [48] Trail Making Test trials 1 (Visual Scanning), 2 (Number Sequencing), and 3 (Letter Sequencing) raw scores; D-KEFS Color-Word Interference Test trials 1 (Color Naming) and 2 (Word Reading) raw scores; and Wechsler Intelligence Scale for Children-IV (WISC-IV) [49] Coding total raw score. The motor speed domain included the D-KEFS Trail Making Test trial 5 (Motor Speed) raw score and Grooved Pegboard [50] left and right hand raw scores. The executive domain contained the RCFT copy trial raw score; CMS Numbers total raw score; D-KEFS Trail Making Test trial 4 (Number-Letter Switching) raw score; D-KEFS Color-Word Interference Test trials 3 (Color-Word Interference) and 4 (Switching) raw scores; and D-KEFS Verbal Fluency Test conditions 1 (Letter Fluency), 2 (Category Fluency), and 3 (Category Switching) raw scores. The attention domain was composed of the Gordon Diagnostic System [51] Continuous Performance Task (CPT) Vigilance and Distractibility trials number of correct and false positive responses. The reaction time domain included the CPT Vigilance and Distractibility trial reaction times. A total domain score was calculated using the average z-scores across all domains. Parent-rating scales included the Behavior Rating Inventory of Executive Function (BRIEF) [52] and the Child Behavior Checklist (CBCL) [53], to examine executive functioning and emotional/behavioral symptoms in daily life, respectively. Between-group

comparisons for cognitive and rating scale data were analyzed via independent-samples T-tests using SPSS version 22, with Bonferroni correction for multiple comparisons.

2.5 Exploratory Analyses

Exploratory analyses were also conducted comparing mTBI participants with (N=13) and without (N=6) previous concussions to determine any potential effects of having one versus multiple injuries on the behavioral measures and extracted cluster activation values.

3. Results

3.1 Neuroradiological Scan Readings

Structural MRI scans were reviewed for incidental findings by a board-certified neuroradiologist. In the mTBI group one participant was noted to have multiple small regions of cystic encephalomalacia compatible with sequelae of remote head trauma; no other TBI-related neuroimaging findings were identified. No acute intracranial abnormalities were identified for any participant in either group. Analyses were repeated with and without the participant with TBI-related neuroimaging findings, without change in the overall pattern of findings.

3.2 N-back Task Performance

Across participants a difference in N-back condition performance was found, $F(2, 74) = 11.827$, $p < 0.001$, demonstrating the expected effect of task difficulty. Using Bonferroni adjustment for multiple comparisons (three comparisons, corrected $p = 0.017$) there was no difference between the 0- and 1-back conditions ($p > 0.05$, 0-back M = 92.4, SD = 11.5; 1-back M = 91.6, SD = 13.8), a difference between 0- and 2-back ($p < 0.001$), where performance was lower on 2-back (M = 81.7, SD = 15.4), and a difference between 1- and 2-back ($p = 0.001$), where performance was also lower on 2-back. Also across participants a difference in N-back condition reaction time was found $F(2, 74) = 60.254$, $p < 0.001$. Using Bonferroni adjustment (three comparisons, corrected p = 0.017) there were reaction time differences between all conditions, 0- (M = 0.993, SD = 0.15) and 1-back (M = 1.093, SD = 0.19), 0- and 2-back (M = 1.228, SD = 0.22), and 1- and 2-back (all $p < 0.001$), with slower reaction time as task difficulty increased. As per study design groups were matched on demographic variables and 2-back performance. In addition, there were no significant differences ($p > 0.05$) for performance or reaction time for any N-back condition (0-, 1-, and 2-back; Table 3). Likewise there were no significant differences in N-back performance or reaction time between mTBI participants with and without previous injury.

3.3 Brain Activation

Within-group examination of task main effects (2-back > 0-back) revealed the expected bilateral frontoparietal activation pattern commonly seen for this task. Between-group comparisons at $p_{crit} = 0.01$, with cluster-level $p_{FWE\text{-}corr} < 0.05$ revealed that the mTBI group showed greater brain activation than controls during the most difficult working memory task condition in three clusters: Cluster 1 was located in the left sub-lobar insula, left middle temporal gyrus, and left superior temporal gyrus (Brodmann Areas (BA) 13, 19, 39); Cluster 2 was located in the left precentral gyrus and left sub-lobar insula (BA 6, 13); and Cluster 3

was located in the right frontal lobe sub-gyral region and right medial frontal gyrus (BA 4, 6) (Figure 1, Table 4). We also examined the data at a more stringent overall $p_{crit} = 0.001$, with cluster-level $p_{uncorr} < 0.05$, and found that Clusters 1 and 2 remained significant, though were reduced in spatial extent. There were no brain regions where controls showed greater activation than mTBI at either significance threshold. No significant differences were found between mTBI with and without previous injury when comparing the activation in the three clusters.

Comparison of the regions in which group differences were seen relative to the main effect activation map for the control group revealed that the mTBI group showed increased activation within typical frontoparietal working memory circuitry, as well as expanded spatial extent of activation outside neural circuitry activated by the control group for this task (Figure 2).

3.4 Correlations between fMRI Activation and N-back Behavioral Data and Time since Injury

There were no correlations between fMRI activation and N-back performance accuracy or reaction time in the overall sample or in the control group alone. In the mTBI group there was a positive correlation between 0-back performance and activation in Cluster 2 at $p_{crit} < 0.001$ ($r(17) = .553$, $p = .014$). Significant correlations were found between time since injury and performance accuracy for 0-back ($r(17) = .483$, $p = .036$) and 1-back ($r(17) = .563$, $p = .012$) but not 2-back ($r(17) = .309$, $p = .198$), such that longer time since injury correlated with better task performance. Time since injury did not correlate with N-back reaction time or fMRI activation.

3.5 Neuropsychological Testing and Rating Scales

No between-group differences were found in cognitive domain scores (all $p > 0.05$, Table 5). On behavioral rating scales mTBI participants had significantly higher levels of parent-reported concern relative to controls on two BRIEF domains: Emotional Control $t(36) = -2.089$, $p = 0.044$ and Organization of Materials $t(36) = -2.078$, $p = 0.045$, and on two CBCL domains: Somatic Problems $t(36) = -2.327$, $p = 0.026$ and Oppositional Defiant Problems $t(36) = -2.294$, $p = 0.028$. However, all group mean domain T-scores were well within the normal range for age (for the overall sample T-scores for BRIEF subscales ranged from 43.1 to 55.9, CBCL subscales ranged from 51.7 to 56.6). In addition, these group differences did not survive Bonferroni correction for multiple comparisons (BRIEF, eight comparisons, corrected p = 0.006; CBCL, six comparisons, corrected p = 0.008). There were no significant differences in cognitive performance or behavioral ratings between mTBI participants with and without previous injury.

Discussion

We found increased working memory task-related brain activation in frontotemporal regions in children and adolescents up to one year post-concussion relative to healthy controls, in the context of comparable fMRI task performance. Groups were not significantly different in cognitive performance or parent behavioral ratings after correction for multiple comparisons.

While there was a trend for greater parent-reported somatic and behavioral symptoms and concerns regarding executive functioning in daily life in the mTBI group, scores remained well within normal limits for age on these scales. These findings extend the limited existing literature which has used fMRI to study pediatric populations in the subacute period after mTBI, and offer evidence of persistent alterations in brain function in adolescents further out from injury than has been examined in prior work.

Examination of brain activation patterns revealed that the mTBI group showed both increased activation within expected working memory circuitry and expanded spatial extent of activation beyond that seen in the control group. This pattern of findings may reflect compensatory brain activation to support working memory performance after mTBI, and is consistent with our group's prior work, where we found increased task-related activation in adult mTBI participants relative to controls in the context of similar task performance, interpreted as reflective of compensatory changes [24, 25]. Similarly, in response to alpha-2 adrenergic challenge we found improved task performance and increased working-memory related activation in adults after mTBI, again suggesting that increased activation in task-related circuitry served a compensatory function [39]. Prior studies in adolescent athletes after sports-related concussion have shown that working memory activation subacutely (~1 week) correlates with post-concussive symptomatology and time to recovery [33, 34]. Pardini et al. [34] found that increased symptom severity at one week post-injury was related to regionally specific hyperactivation during working memory, despite a lack of association between post-concussive symptoms and task performance. Of particular interest, Lovell et al.'s work demonstrated that concussed adolescent athletes who showed greatest hyperactivation in Brodmann Area (BA) 6 in their first week post-injury showed the longest recovery times [33]. BA 6 was among the regions showing significant hyperactivation in the mTBI group relative to controls in the current study, even much later after injury. As noted, about 68% of the mTBI group in the present cohort reported having experienced prior concussions. Taken together, the current data and the results of prior studies suggest that increased brain activation, including in BA 6, may reflect persistent functional brain changes which may be related to injury, and that activation in these brain regions may be related to prolonged recovery from injury. This could explain the need for altered brain activation to sustain normal working memory performance (i.e., a compensatory model).

In contrast, Elbin et al. [54] studied high school and college athletes with a history of multiple concussions, after complete resolution of post-concussive symptoms (mean 9 months post-injury, range 3–26 months), and found no difference from nonconcussed athlete controls in working memory-related brain activation. However, their post-concussion group showed significantly worse N-back performance accuracy (1-, 2-, and 3-back) than controls. A strength of the current study was that mTBI participants and controls were matched at the group level for 2-back performance accuracy and key demographic variables (i.e., age, sex, estimated intelligence, and maternal education), allowing examination of brain activation differences in the context of comparable task performance and similar demographic backgrounds. In this context, the finding of Elbin et al. of no between-group activation differences may reflect the poorer task performance in the concussion group (i.e., a failure to effectively compensate for multiple concussions).

Krivitsky et al. [32] also examined working memory performance after pediatric mTBI (on average one month post-injury, range 8–82 days), in a cohort who all had at least some persistent post-concussive symptoms, though none had experienced a prior concussion. They used a somewhat different N-back task which also included a response inhibition component. In their cohort, brain activation differences were only found when inhibitory processes were introduced, with mTBI participants showing greater cerebellar activation than controls. Greater cerebellar activation was correlated with greater post-concussive symptoms in the mTBI group. mTBI and control groups did not differ in neuropsychological performance, but did differ on rating scales of executive difficulties in daily life. Unfortunately, in-scanner task performance data were not available, so it is unclear to what degree brain activation differences (or lack thereof for the purely working memory task components) might be related to the ability of the mTBI group to perform comparably to controls. However, the finding of greater activation correlating to greater symptoms is consistent with the other related work described above.

Yang et al. [55] found reduced activation during auditory orienting in adolescents within a month of mTBI relative to controls, in the context of suggestive but not significant cognitive decrements. They interpreted their findings as potentially indicating that fMRI may be a more sensitive marker of brain dysfunction after mTBI than more commonly used clinical measures such as neuropsychological assessment and structural MRI. Keightley et al. [31] examined working memory performance after mTBI (average 41 days post injury, range 9–90 days) using an externally ordered working memory task. They found poorer task performance and lower brain activation in the mTBI group relative to controls, consistent with prior work using this task in adults after mTBI [26, 27]. Keightley et al. interpreted their findings as suggesting that youth may be less able to effectively engage cognitive compensatory strategies after mTBI. Of note, patients in the Keightley et al. study on average reported moderate levels of post-concussive symptoms. As the authors note, it is possible that the pattern of cognitive (and imaging) findings would change with symptom resolution. Our findings may indicate that such cognitive compensation may be possible at a longer interval after injury, a hypothesis partly supported by our data showing stronger performance on aspects of the N-back task by those further out from injury. Longitudinal investigations will be ideal to examine the time course of and relationship between changes in brain activation, cognitive performance, and post-concussive symptoms after pediatric mTBI. It may be that in the initial post-injury period poorer cognitive performance is accompanied by reduced brain activation, but that over time compensatory changes result in improved task performance and increased brain activation. The relationships between post-concussive symptoms, cognition, and brain function also require further investigation.

Limitations of the current study include the cross-sectional design, in which only post-injury information was collected. It is therefore possible that differences seen could reflect some baseline difference that predisposed individuals to experiencing TBI or having persistent post-injury functional changes, though this seems unlikely given the consistency of our findings with other related work, as noted above. The current sample was a convenience sample recruited from the community and local physicians. It is therefore possible there may have been a recruitment bias towards participants with persistent concerns. Alternative recruitment approaches, for example using consecutive referrals from a concussion clinic,

might result in differing findings. The current study also lacked detailed data regarding prior injuries and the presence or absence of persistent post-concussive symptoms, which would have been useful for correlation with brain activation and behavioral data. In our ongoing longitudinal studies such data is being gathered, and will hopefully further clarify these relationships. While comparable to other studies cited, our sample size was modest; a larger cohort would be expected to have increased power to detect clinically meaningful differences between individuals after mTBI and controls and correlations between dependent variables and injury-related factors. To examine the importance of statistical power for these findings, we examined the data at two thresholds, including a more lenient overall p_{crit} of 0.01 with cluster-level FWE correction and a more stringent overall p_{crit} of 0.001without the cluster-level correction. As described, two of three clusters were significant at both thresholds, further strengthening confidence in the findings. As discussed above, most of our sample had experienced multiple concussions, and so these findings may not generalize to a sample of individuals experiencing a first mTBI. However, in the current cohort there were no significant differences between those with and without prior injury on dependent variables of interest, though group sizes were small.

Despite the limitations noted above, our finding of greater working memory-related activation in mTBI participants than controls up to a year post-injury suggests that further investigation of the potential remote consequences of even mild brain injury is warranted. Differences in working memory-related brain activation were found in the mTBI group 3–12 months after injury, at a time when prior cognitive studies have shown most individuals should have experienced clinical recovery. Indeed, cognitive and behavioral performance did not differ between our mTBI and control groups, a common finding in mTBI studies. These data suggest that functional neuroimaging may prove to be a more sensitive indicator of post-concussive effects than traditional neuropsychological tests, allowing detection of differences in brain function between individuals after mTBI and controls even in the absence of objective cognitive deficits, and even after the subacute period. To date, such work in pediatric populations has been limited, with much more data available in adults or in college-age athletes. Greater understanding of potentially differential responses to brain injury in the developing brain is clearly needed. Future work using longitudinal study designs will be very informative to monitor such differences over time and examine variables which may predict good versus poor clinical recovery and functional activation. Ideally such studies would also include pre-injury baseline data, though this is more challenging to obtain. Further investigation is needed to clarify the relationship of these brain activation changes to functional and symptom status, and to more closely examine potential risk factors for persistent post-concussive changes in brain function in children and adolescents, including demographic, medical, or genetic differences between individuals. Such information could have important implications for clinical management, including implementation of treatment and rehabilitation approaches where appropriate, as well as for decisions regarding safety of return to athletic or other activities.

Acknowledgments

The authors thank our MRI technologist colleagues at the Indiana Institute for Biomedical Imaging Sciences for their assistance in assuring successful MRI scans, and also thank Lindsey Shine and Kimberly Campbell for their

contributions to this project. We are also very grateful to our participants and their families for their time and effort. This work was supported by a grant from the Indiana State Department of Health Spinal Cord and Brain Injury Fund Research Grant Program and by a Project Development Team within the ICTSI NIH/NCRR Grant Number RR025761.

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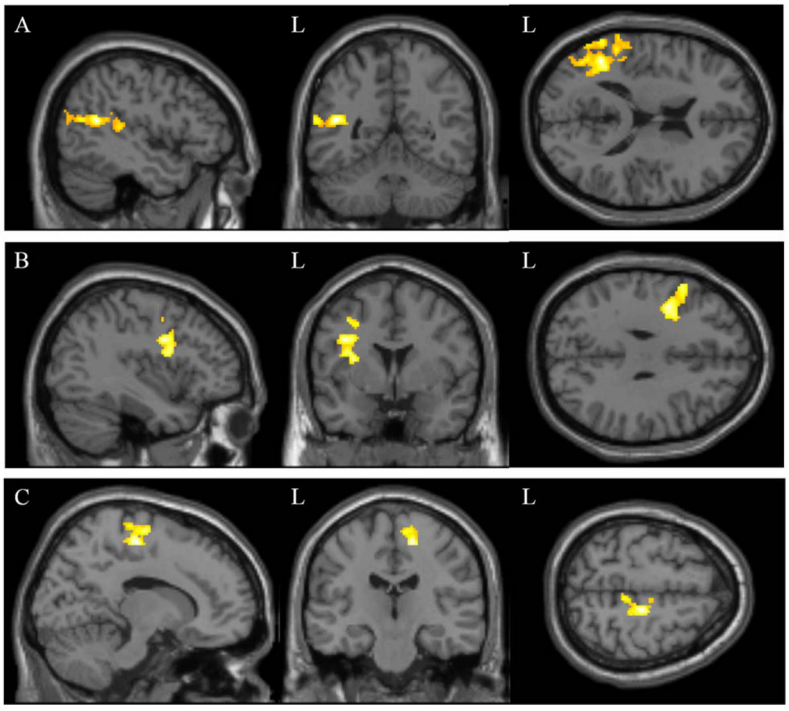

Figure 1.

Regions showing significantly greater activation in mTBI compared to healthy control group (p_{crit} = 0.01; cluster-level $p_{FWE\text{-}corr}$ < 0.05). A) Cluster 1: left sub-lobar insula, left middle temporal gyrus, and left superior temporal gyrus (Brodmann Areas (BA) 13, 19, 39); B) Cluster 2: left precentral gyrus and left sub-lobar insula (BA 6, 13); and C) Cluster 3: right frontal lobe sub-gyral region and right medial frontal gyrus (BA 4, 6).

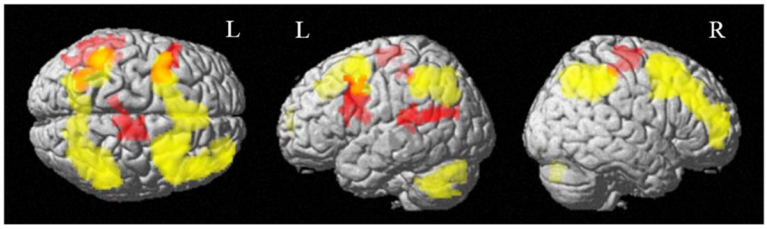

Figure 2.

Comparison of regions showing significantly greater activation in mTBI compared to healthy controls to main effect of task in control group (p_{crit} = 0.01; cluster-level $p_{FWE\text{-}corr}$ < 0.05). Yellow indicates main effect of task (2-back > 0-back) in healthy control group, while red indicates regions showing greater activation in mTBI than controls (also displayed in Figure 1). Note both increased activation within typical working memory circuitry as well as expanded spatial extent of activation outside of regions activated by controls.

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Table 1

mTBI Injury Characteristics

Participant	Age	Sex	Months since injury	Cause of injury	Length of LOC	Number of prior mTBIs*
1	16	Male	6	Snowboarding	Few seconds	0
2	15	Male	12	Football	Few seconds	>1
3	14	Female	8	Bicycle	No LOC	1
4	15	Male	7	Hockey	Unsure if LOC	1
5	15	Female	6	Hockey	No LOC	1
6	10	Male	6	ATV	Unsure if LOC	2
7	16	Male	3	Football	No LOC	1–2
8	13	Male	6	Hockey	No LOC	1
9	15	Female	9	ATV	No LOC	0
10	15	Male	11	Football	No LOC	1
11	15	Male	10	Football	No LOC	1–2
12	16	Male	6	Track	No LOC	0
13	15	Female	6	Roller Blading	No LOC	1–2
14	14	Female	6	Softball	No LOC	0
15	15	Male	7	Baseball	No LOC	0
16	16	Male	6	Soccer	No LOC	1
17	16	Female	6	Soccer	Few seconds	0
18	15	Male	11	Football	No LOC	1
19	14	Male	11	Football	No LOC	1

ATV=All-terrain vehicle LOC=Loss of consciousness

*Per participant/parent report. Participant 2 reported being told by a doctor that he had sustained multiple prior concussions, but could provide no further detail. Participants 7, 11, and 13 were inconsistent in reporting, and there was insufficient detail to determine whether 1 or 2 prior mTBIs had occurred.

Table 2

Sample Demographics

	Healthy controls (N=19)	mTBI (N=19)
Age (years)	14.0 (1.7)	14.7 (1.4)
Sex (M,F)	10,9	13,6
WASI Full Scale IQ	105.6 (11.1)	111.2 (10.1)
Maternal Education (years)	14.9 (2.5)	15.2 (2.0)
Time since mTBI (months)	N/A	7.5 (2.4)

Values are mean (sd). There were no significant differences between groups (all $p > 0.05$).

Table 3

N-back Performance across Groups

N-Back Performance	Healthy controls (N=19)	mTBI (N=19)
0-Back Total Correct (%)	89.6 (14.4)	95.2 (6.8)
1-Back Total Correct (%)	88.5 (17.2)	94.7 (8.7)
2-Back Total Correct (%)	78.6 (15.0)	84.7 (15.5)
0-Back Reaction Time (s)	1.0 (0.1)	1.0 (0.2)
1-Back Reaction Time (s)	1.1 (0.2)	1.0 (0.2)
2-Back Reaction Time (s)	1.3 (0.2)	1.2 (0.2)

Values are mean (sd), corrected for guessing. There were no significant differences between groups (all $p > 0.05$).

Table 4

Statistically Significant fMRI Clusters

	Cluster-level				Peak-level				
Cluster	$p_{FWE\text{-}corr}$	$q_{FDR\text{-}corr}$	k_E	p_{uncorr}	**T**	**Z**	**Peak MNI coordinates (x y z)**	**Region description**	**Brodmann Area (BA)**
Overall $p_{crit} < 0.01$, Cluster-level $p_{FWE\text{-}corr} < 0.05$									
1	0.001	0.001	812	<0.001	4.80	4.19	(−46, −52, 16)	Left Sub-lobar Insula; Left Middle Temporal Gyrus; and Left Superior Temporal Gyrus	13, 19, 39
2	0.001	0.001	744	<0.001	4.32	3.85	(−32, 0, 14)	Left Precentral Gyrus and Left Sub-lobar, Insula	6, 13
3	0.011	0.007	535	<0.001	4.34	3.87	(14, −20, 58)	Right Frontal Lobe, Sub-Gyral and Right Medial Frontal Gyrus	4, 6
Overall $p_{crit} < 0.001$, Cluster-level $p_{uncorr} < 0.05$									
1	0.532	0.594	44	0.038	4.80	4.19	(−46, −52, 16)	Left Superior Temporal Gyrus	39
2	0.063	0.129	102	0.003	4.32	3.85	(−32, 0, 14)	Left Precentral Gyrus and Left Sub-lobar, Insula	6, 13

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Table 5

Domain Z-scores

Domain	mTBI (N=19)
Processing Speed	0.18 (0.59)
Motor Speed	0.26 (0.51)
Attention	0.07 (0.80)
Executive	0.23 (0.44)
Reaction Time	−0.45 (1.62)
Memory	0.25 (0.56)
Total	0.09 (0.53)

Values are z-scores (sd). Z-scores were calculated using the healthy control group mean and sd.